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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,180	02/12/2004	Marc Beauregard	15493-2US	3080

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,180	BEAUREGARD ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (Claims 1-10) in the reply filed on 10/27/2005 is acknowledged.

2. Claims 11-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/27/05.

3. Applicant elected without traverse of the following species:

A.) Thermostable DNA polymerase, and more particularly, Thermococcus litoralis;

B.) 0.05 to 1.0 molar for molar concentration;

C.) 1-propanol;

D.) Transition;

E.) 1 to 10 mutations per nucleotides sequence having one hundred (100) nucleic acids.

Accordingly, the non-elected species are withdrawn from the corresponding claims.

4. Claims 1-17 are currently pending;

Claims 11-17 have been withdrawn;

Claims 1-10 are being examined in this application.

Priority

5. This application claims priority to provisional application 60/446,518 filed on 2/12/2003.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1-propanol used in PCR reaction with certain thermo polymerases (Vent$_r$® or Taq) and DNA template (MB-1 His gene) to generate mutations, does not reasonably provide enablement for all alcohols (such as ethanol, 2-aminoethanol, butanol, etc.), all polymerases as well as all DNA templates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;

6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims

The breadth of the claims seems to encompass all polymerization reactions using at least one DNA polymerase (would read on all possible DNA polymerases) in the presence of at least one alcohol (would read on all possible chemical entities that are classified under alcohol). The claims would also read on any possible polymerization reaction conditions (including various buffer conditions as well as any combinations of other ingredients.) No structural and/or functional limitations are provided for the claimed genus of alcohol, polymerases and reaction conditions.

The nature of the invention

The nature of the invention in claims 1-10 is a method of generating mutations in PCR products (DNA fragments) by adding alcohols to the reaction mixtures.

The state of the prior art/ The predictablility or lack thereof in the art

Error-prone PCR is a popular method to generate mutations in DNA to use for various applications. Several measures could be used to increase the error rate in a PCR reaction including 1.) varying buffer composition (e.g. high magnesium concentration, a high pH, or the addition of $MnCl_2$); 2.) increasing the amount of polymerase; 3.) Decreasing template amount; 4.) increasing number of cycles or varying cycling conditions; 5.) biasing the dNTPs pools; 6.) or by pre-treating the template chemically. Each of the measure could be used or in combination thereof to induce mutations in PCR products relative to the original template. Addition of

denaturing compound such as alcohol could effect the enzymatic function and/or property of a protein such as a DNA polymerase.

However, the effect of various chemical compounds on protein folding structures and enzymatic activities are highly unpredictable. It is not know how various alcohol molecules (such as propanol, ethanol, butanol, etc.) affect protein function and/or properties. In addition, the ultimate affect of alcohol on various polymerases (Vent, Taq, for examples) would be unpredictable. For example, Claveau et al (DNA and Cell Biology. Vol. 23: 789-795) teach using propanol in PCR reactions with various thermo polymerases. The study shows that while PCR reaction with Vent polymerase generated mutations with the addition of propanol in the reaction mixture, reaction with a closely related polymerase (Deep Vent) does not respond to the addition of propanol (See Result and Discussion of the reference). Furthermore, various alcohols would also have different effects on various polymerases. For example, Lu et al (Trends in Genetics. Vol. 9: 297) teach a method of adding glycerol (an alcohol) in PCR reaction to improve PCR reaction of Taq polymerase and improve reaction efficiency and specificity (See Figure 1 of the reference). This effect of glycerol would contradict the instant claimed invention that using alcohol to promote mutations in a PCR reaction. Lastly, different templates would also have different effects in the outcome of a PCR reaction. For example, Lu et al teach that certain DNA template could not be amplified (See 2nd paragraph of the reference), and therefore would not allow the generation of mutated PCR products.

The level of one of ordinary skill

The level of skill would be high in order to carry out the various PCR reactions.

The amount of direction or guidance present

The only guidance presented in the instant specification is directed to PCR amplification reactions by using MB-1 His gene (384 bp) with 1-propanol and Taq, or Vent polymerase. There are no guidance described for using other alcohols and other DNA polymerase to generate mutations. Since concentrations of the alcohols used in the PCR reaction mix is important to the success of the method, and the experimentally determined critical alcohol concentration is unpredictable, detailed guidance should be provided for all the species claimed in the entire genus of alcohol.

The presence or absence of working examples

The only presence of a working example is the example listed on Pages 17-27 for the PCR reaction using 1-propanol with certain polymerases as discussed above. Since the effects of various alcohols on various polymerases are different (may or may not induce mutation), working examples that are structurally or functionally representative of the entire genus of the claimed methods would be required.

The quantity of experimentation needed

Due to the unpredictabilities of the effects of various alcohol on different polymerases under different reaction conditions (as discussed supra), and the lack of guidance in the instant specification, large quantities of experimentation would be required. The art has demonstrated that not only the same alcohol (e.g. 1-propanol) would have different effects on different polymerases (in term of inducing mutation), but also different alcohols (e.g. propanol vs. glycerol) would induce different effects on the same polymerase (Taq polymerase) as discussed supra. In addition, to achieve mutations, certain alcohol concentrations must be used. These concentration requirements appear to be not predictable and must be determined by

experimentations. Since the instant specification only provides guidance for one example of (using propanol with Vent polymerase), undue experimentations must be carried out to practice the entire genus of claimed method.

Conclusion

Due to the large quantity of experimentation necessary to determine each specific reaction condition for each one of the combination of an alcohol and a polymerase as well as a specific reaction buffer and/or reagent; the lack of direction/guidance presented in the specification regarding the specific requirements for reaction conditions; the predictability of the effects of various alcohol on different polymerization reactions as established by the state of the prior art; the breadth of the claims to establish any structural or functional limitations, undue experimentations would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Written Description Rejection

8. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method comprising submitting DNA template to polymerization reaction with DNA polymerase in the presence of at least one alcohol, which would cause mutagenesis during the polymerization reaction.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

Written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not case involves question of priority, since requirement applies to all inventions including chemical inventions, and since the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide description of compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

Although the instant specification recites examples of using 1-propanol in PCR reaction with Vent®$_r$ or Taq polymerase and a particular DNA template to generate mutated PCR products, the instant specification and/or the aforementioned claims do not provide adequate written description to show possession of the entire genus of alcohol, DNA polymerase and/or DNA template that would be used in the claimed method. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The only factor present in this case is that the alcohol is a chemical entity comprising a –OH group, which does not provide any functional and/or property limitation since chemical compounds with a –OH group could have entirely different chemical structures and/or properties.

The instant claims do not provide any limitation on the chemical structure, property or other distinguishing features of each genus: alcohol, polymerase and/or DNA template (and/or

other reagents). Not only would each species within each genus have different structure and/or function from each other, but each genus would also differ from each other in term(s) of structure and/or function. For example, each species of method (in terms of a specific alcohol, a specific DNA polymerase and/or a specific DNA template) would have different property and/or function. A combination of certain alcohol(s) and DNA polymerase(s) may not induce mutation in a PCR reaction as discussed before, for example. In addition, factors such as alcohol concentration, the amount of DNA template, the type of DNA polymerase, proportions of dNTPs are also critical in successfully carrying out the claimed invention (to generate random mutations in PCR products). The example (species) provided in the instant application is not sufficient to represent the entire genus of claimed method using various alcohols, DNA polymerases, DNA templates, and/or other reagents, because the example does not provide the necessary structural and functional limitations on the entire genus.

As discussed above, the skilled artisan cannot envision the detailed steps and/or requirements the encompassed genus of method that use various alcohol, DNA polymerase and DNA template, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of creating such composition. Adequate written description requires more than a mere statement that it is part of the invention and reference to a possibility of creating it. The composition itself is required.

Therefore, the instant Claims 1-10 do not meet the written description provision of 35 U.S.C. 112, first paragraph.

9. The following is a quotation of the **second paragraph of 35 U.S.C. 112**:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "at least one alcohol in concentration sufficient to lower the fidelity of said DNA polymerase." The phrase "concentration sufficient to" is indefinite and is not clearly defined in either the specification or the claim. Concentration of the recited alcohol is critical to the success of the claimed polymerization reaction as described in the instant specification (page 21). Without a clear definition or range of the concentration, one of skill in the art would not be able to clearly define the metes and bounds of the claimed invention. For example, trace amount of alcohol carried over from DNA purification procedure to the PCR reaction would be readable on the claimed invention.

Claim 1 also recites the phrase "to lower the fidelity of said DNA polymerase". From which, the phrase "to lower the fidelity" is not clearly defined in either the specification or the claim. How much lower should the fidelity of a polymerase be?

Claim 10 recite the phrase "under conditions that allow for controlling mutational bias", which is indefinite and unclear. The instant specification or the claims do not provide specific definition for "conditions" and "mutational bias". Without precise and defined reaction parameters, one skilled in the art would not be able to determine what PCR conditions are within or outside the boundary of the claimed invention.

Claim 2 recites the limitation "said mutation". There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation "said mutated nucleic acid sequence". There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Claims 1-10 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL
Art Unit 1639
12/07/2005

PRIMARY EXAMINER